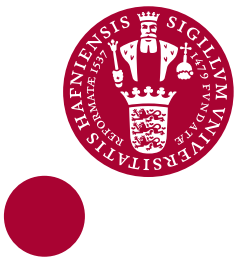

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Differential Impact of Heart Failure With Reduced Ejection Fraction on Men and Women

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ABSTRACT

BACKGROUND Heart failure (HF) trials initiated in the last century highlighted many differences between men and women. Of particular concern was undertreatment of women compared with men, but much has changed during the past 20 years.

OBJECTIVES This study sought to identify these changes, which may give a new perspective on the management of, and outcomes in, women with HF.

METHODS The study analyzed 12,058 men and 3,357 women enrolled in 2 large HF with reduced ejection fraction (HFrEF) trials with near identical inclusion and exclusion criteria and the same principal outcomes. Outcomes were adjusted for other prognostic variables including N-terminal pro-B-type natriuretic peptide.

RESULTS Women were older and more often obese than men were, had slightly higher systolic blood pressure and heart rate, and were less likely to have most comorbidities, except hypertension. Women had more symptoms and signs (e.g., pedal edema 23.4% vs 19.9%; $p < 0.0001$) and worse quality of life—median Kansas City Cardiomyopathy Questionnaire Clinical Summary Score 71.3 (interquartile range: 53.4 to 86.5) versus 81.3 (interquartile range: 65.1 to 92.7; $p < 0.0001$)—despite similar left ventricular ejection fraction and N-terminal pro-B-type natriuretic peptide. However, women had lower mortality (adjusted hazard ratio: 0.68; 95% confidence interval: 0.62 to 0.74; $p < 0.001$) and risk of HF hospitalization (hazard ratio: 0.80; 95% confidence interval: 0.72 to 0.89; $p < 0.001$). Diuretics and anticoagulants were underutilized in women. Device therapy was underused in both men and women, but more so in women (e.g., defibrillator 8.6% vs. 16.6%; $p < 0.0001$).

CONCLUSIONS Although women with HFrEF live longer than men, their additional years of life are of poorer quality, with greater self-reported psychological and physical disability. The explanation for this different sex-related experience of HFrEF is unknown as is whether physicians recognize it. Women continue to receive suboptimal treatment, compared with men, with no obvious explanation for this shortfall. (J Am Coll Cardiol 2019;73:29–40)

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

AF = atrial fibrillation

ARB = angiotensin receptor blocker

CAD = coronary artery disease

CI = confidence interval

CV = cardiovascular

eGFR = estimated glomerular filtration rate

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

HRQL = health-related quality of life

IRR = incidence rate ratio

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVEF = left ventricular ejection fraction

MI = myocardial infarction

MRA = mineralocorticoid receptor antagonist

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

SBP = systolic blood pressure

A series of trials initiated in the last century highlighted many differences between men and women with heart failure (HF) (1–8). Of particular concern in these trials and other studies was the suggestion that, in common with other cardiovascular (CV) conditions, women were less well treated than men were (1–13). Since those trials were initiated, much has changed in the assessment and management of patients with HF. Natriuretic peptides are now measured routinely (14,15). Beta-blockers are recommended for all patients with HF with reduced ejection fraction (HFrEF), whereas in the largest previous comparison of men and women were used in only 55% of patients (7). Similarly, the indication for mineralocorticoid receptor antagonists (MRAs) has broadened to patients with mild symptoms, as has the indication for cardiac resynchronization therapy (the effectiveness of which had not even been demonstrated when many of the previous studies were conducted) (14,15). All of these changes may give a new perspective on the management of, and outcomes in, women with HFrEF.

Herein, we compared women and men with HF enrolled in the 2 most recent and largest randomized controlled trials of pharmacological therapy in patients with HFrEF (16,17).

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METHODS

TRIALS AND PARTICIPANTS. The inclusion and exclusion criteria of the PARADIGM-HF (Prospective comparison of ARNI [Angiotensin Receptor Neprilysin Inhibitor] with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) and ATMOSPHERE (Aliskiren Trial to Minimize OutcomeS in Patients with Heart failure) trials were almost identical (16,17). Briefly, patients were eligible at screening if ≥18 years of age, New York Heart Association (NYHA) functional class II to IV, left ventricular ejection fraction (LVEF) ≤35% (changed from ≤40% in the PARADIGM-HF trial by amendment), elevated natriuretic peptide level, taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), beta-blocker (unless contraindicated or not tolerated), and MRA, if indicated. The natriuretic peptide eligibility criteria were plasma B-type natriuretic peptide ≥150 pg/ml or N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥600 pg/ml; patients hospitalized in the preceding 12 months were eligible with a lower level: B-type natriuretic peptide ≥100 pg/ml or NT-proBNP ≥400 pg/ml.

Exclusion criteria included symptomatic hypotension or systolic blood pressure (SBP) <95 mm Hg (<90 mm Hg in the ATMOSPHERE trial), estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 (<35 ml/min/1.73 m^2 in the ATMOSPHERE trial), and potassium >5.4 mmol/l (>5.2 mmol/l in the ATMOSPHERE trial). The trial was approved by ethics committees at 1,043 participating centers in 47 countries in the PARADIGM-HF trial and 789 centers in 43 countries in the ATMOSPHERE trial, and all patients provided written informed consent.

On trial entry, ACE inhibitor or ARB therapy was stopped and patients entered a sequential run-in, first receiving enalapril followed by sacubitril/valsartan in the PARADIGM-HF trial and enalapril followed by the combination of enalapril plus aliskiren in the ATMOSPHERE trial. Patients tolerating both run-in periods were randomly assigned to double-blind therapy with sacubitril/valsartan or enalapril in a 1:1 ratio in the PARADIGM-HF trial or enalapril, aliskiren, or both drugs in a 1:1:1 ratio in the ATMOSPHERE trial.

The median duration of follow-up was 26.6 months in the PARADIGM-HF trial (minimum 1 day,

membership fees from Boehringer Ingelheim and Vifor Pharma. Dr. Desai has served as a consultant for Novartis, Abbott, AstraZeneca, DalCor, Relypsa, Regeneron, Signature Medical, Boston Scientific, and Boehringer Ingelheim. Dr. Packer has served as a consultant for Actavis, Amgen, Boehringer Ingelheim, AstraZeneca, Cardiorentis, Daiichi-Sankyo, Gilead, Relypsa, Sanofi, Takeda, and Synthetic Biologics. Dr. Rouleau has served as a consultant for Novartis and AstraZeneca. Dr. Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Bristol-Myers Squibb, Celladon, Gilead, GlaxoSmithKline, Ionis, LoneStar Heart, Mesoblast, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, Sanofi Pasteur, and Theracos; and has served as a consultant for Akros, Alnylam, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Corvia, Gilead, GlaxoSmithKline, Ironwood, Merck, Novartis, Pfizer, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, Abiomed, and Janssen. Dr. Swedberg has served as a consultant for AstraZeneca, Novartis, and Servier. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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TABLE 1 Baseline Characteristics of Men and Women With HFrEF

	Women (n = 3,357)	Men (n = 12,058)	p Value
Age, yrs	65.10 ± 11.9	63.10 ± 11.5	<0.0001
Age group			<0.001
≤40 yrs	104 (3.1)	464 (3.8)	
41–55 yrs	584 (17.4)	2,374 (19.7)	
56–70 yrs	1,436 (42.8)	5,832 (48.4)	
>70 yrs	1,233 (36.7)	3,388 (28.1)	
Region			<0.001
North America	132 (3.9)	647 (5.4)	
Latin America	698 (20.8)	1,854 (15.4)	
Western Europe and other	733 (21.8)	3,221 (26.7)	
Central Europe	1,113 (33.2)	3,657 (30.3)	
Asia-Pacific	681 (20.3)	2,679 (22.2)	
Race			<0.001
Caucasian	2,128 (63.4)	8,008 (66.4)	
Black	166 (4.9)	371 (3.1)	
Asian	664 (19.8)	2,609 (21.6)	
Others	399 (11.9)	1,070 (8.9)	
SBP, mm Hg	123.9 ± 17.0	122.0 ± 16.7	<0.0001
Heart rate, beats/min	72.8 ± 11.7	71.9 ± 12.4	<0.0001
BMI, kg/m^2	27.1 (24–32)	27.1 (24–31)	0.136
Weight category*			<0.001
Underweight	118 (3.5)	189 (1.6)	
Normal	1,005 (30.0)	3,560 (29.6)	
Overweight	1,106 (33.0)	4,764 (39.6)	
Obese	1,120 (33.4)	3,524 (29.2)	
Comorbidities			
Atrial fibrillation (history)	1,093 (32.6)	4,388 (36.4)	<0.0001
Hypertension	2,369 (70.6)	7,903 (65.5)	<0.0001
Coronary artery disease	1,444 (43.0)	6,755 (56.0)	<0.0001
Myocardial infarction	1,007 (30.0)	5,474 (45.4)	<0.0001
Unstable angina	307 (9.1)	1,414 (11.7)	<0.0001
Stable angina	698 (20.8)	2,409 (20.0)	0.299
Prior PCI	445 (13.3)	2,735 (22.7)	<0.0001
Ischemic etiology	24.2	35.2	
Nonischemic	2.3	3.5	
Prior CABG	226 (6.7)	2,055 (17.0)	<0.0001
Ischemic etiology	12.9	27.6	
Nonischemic	0.7	1.0	
Clinically significant valve disease	178 (5.3)	553 (4.6)	0.084
Cerebrovascular disease	362 (10.8)	1,574 (13.1)	0.004
Stroke	248 (7.4)	969 (8.0)	0.218
Known carotid artery disease	69 (2.1)	443 (3.7)	<0.0001
Peripheral arterial disease	93 (2.0)	719 (6.0)	<0.0001
Prior lower limb revascularization	28 (0.8)	233 (1.9)	<0.0001
Intermittent claudication	78 (2.3)	596 (4.9)	<0.0001
Asthma	173 (5.2)	354 (2.9)	<0.0001
COPD	285 (8.5)	1,582 (13.1)	<0.0001
Diabetes	1,041 (31.0)	3,810 (31.6)	0.517
Renal disease	392 (11.7)	1,671 (13.9)	0.001
Cancer	153 (4.6)	505 (4.2)	0.349
Anemia†	700 (20.9)	2,610 (21.7)	0.3221
Lifestyle habits			
Smoking status			<0.001
Never smoked	2,694 (80.3)	5,427 (45.0)	
Ex-smoker	456 (13.6)	4,729 (39.2)	
Current smoker	207 (6.2)	1,902 (15.8)	
Alcohol, U/day			<0.001
<1	3,269 (97.4)	10,273 (85.2)	
1–2	79 (2.4)	1,442 (12.0)	
>2	8 (0.2)	342 (2.8)	

Values are mean ± SD, n (%), median (interquartile range), or %. *29 were missing. †Hemoglobin <130 g/l (men), <120 g/l (women)

BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; HFrEF = heart failure with reduced ejection fraction; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

Continued in the next column

maximum 4.2 years) and 36.7 months (minimum 1 day, maximum 6.2 years) in the ATMOSPHERE trial.

OUTCOMES. The primary outcome for both trials was the composite of first HF hospitalization or CV death. In this study, we analyzed the primary outcome, its components, sudden death, pump failure death, non-CV death, and all-cause death in women compared with men. We have also reported recurrent hospitalizations for HF, all CV, non-CV, and all causes. All events except non-HF, non-myocardial infarction (MI), and nonstroke CV hospitalizations, and non-CV hospitalizations were adjudicated by the same clinical endpoint committee using prespecified criteria. In both trials, health-related quality of life (HRQL) was measured at baseline in 13,061 patients using the Kansas City Cardiomyopathy Questionnaire (KCCQ) score, which is scored from 0 to 100, with lower scores indicating a poorer HRQL (18). General quality of life was measured using the EQ-5D-3L in the PARADIGM-HF trial.

STATISTICAL ANALYSIS. Baseline characteristics of patients are reported as mean ± SD, proportions, or median (interquartile range). Statistical tests employed were 2-sample Student's *t* test, chi-square test, and Mann-Whitney *U* test, respectively.

Competing-risks regression, using the Fine-Gray method, was used to assess the outcomes. The primary outcome and CV death were analyzed accounting for the competing risk of non-CV death. First, HF hospitalization was analyzed accounting for the competing risk of all-cause death. Sudden deaths were analyzed accounting for the competing

TABLE 2 Heart Failure: Clinical Characteristics, Investigations, and Treatment in Men and Women With HFrEF

	Women (n = 3,357)	Men (n = 12,058)	p Value
HF etiology			<0.001
Ischemic	1,677 (50.0)	7,289 (60.5)	
Nonischemic	1,494 (44.5)	4,277 (35.5)	
Other	186 (5.5)	492 (4.1)	
Time since HF diagnosis			<0.001
<1 yr	1,168 (34.8)	3,716 (30.8)	
1–5 yrs	1,267 (37.7)	4,558 (37.8)	
>5 yrs	922 (27.5)	3,780 (31.4)	
NYHA functional class*			<0.001
I	92 (2.7)	470 (3.9)	
II	2,182 (65.0)	8,577 (71.2)	
III	1,046 (31.2)	2,915 (24.2)	
IV	37 (1.1)	83 (0.7)	
Prior hospitalization for HF	1,951 (58.1)	7,511 (62.3)	<0.0001
LVEF, %	29.6 ± 5.9	28.8 ± 6.0	<0.0001
KCCQ clinical summary score	71.3 (53.4–86.5)	81.3 (65.1–92.7)	0.001
Symptoms/signs			
Dyspnea at rest	204 (6.1)	408 (3.4)	<0.0001
Dyspnea on effort	2,976 (88.7)	10,191 (84.7)	<0.0001
Orthopnea	290 (8.6)	681 (5.7)	<0.0001
PND	237 (7.1)	519 (4.3)	<0.0001
Edema	787 (23.4)	2,403 (19.9)	<0.0001
Rales			<0.001
Basilar only	350 (10.4)	947 (7.9)	
Greater than one-third of lung field	9 (0.3)	59 (0.5)	
Third heart sound	341 (10.2)	1,048 (8.7)	0.009
JVD	365 (10.9)	1,112 (9.2)	0.004
ECG findings			
Atrial fibrillation	732 (21.8)	2,905 (24.1)	0.006
LBBB	750 (22.3)	2,332 (19.3)	0.0001
RBBB	182 (5.4)	956 (7.9)	<0.0001
QRS duration, ms	104 (86–140)	110 (94–140)	<0.0001
Laboratory investigations			
NT-proBNP, pg/ml	1,448 (801–2,805)	1,406 (761–2,770)	0.158
Hemoglobin, g/l	129.9 ± 14.4	141.0 ± 15.7	<0.0001
Creatinine, μmol/l	81.0 ± 21.6	100.0 ± 25.5	<0.0001
eGFR, ml/min/1.73 m^2	68.2 ± 25.0	71.2 ± 21.3	<0.0001
eGFR <60 ml/min/1.73 m^2	1,267 (37.7)	3,643 (30.2)	<0.001
Baseline treatments and prior interventions			
Diuretic	2,698 (80.4)	9,638 (79.9)	0.574
Loop diuretics†‡	2,523 (75.2)	9,135 (75.8)	0.4721
Thiazides†‡	265 (7.9)	789 (6.5)	0.0061

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risk of all nonsudden death and pump failure deaths were analyzed accounting for the competing risk of deaths not caused by pump failure. Non-CV deaths were analyzed accounting for the competing risk of all CV death. Fatal and nonfatal MI and strokes were analyzed accounting for the competing risk of all-cause death not due to MI or stroke. Along with the crude hazard ratios (HRs), we report adjusted HRs from models including age, heart rate, SBP, NT-proBNP, body mass index, NYHA functional class, LVEF, and eGFR. HF hospitalization was additionally adjusted for previous HF hospitalization. All models were adjusted for randomized treatment and region.

Recurrent hospitalizations (for HF, CV, non-CV, and all causes) were analyzed using a negative binomial regression model. Both crude incidence rate ratios (IRRs) and IRRs adjusted for the variables mentioned previously are reported. All analyses were conducted using STATA version 14 (StataCorp, College Station, Texas).

RESULTS

There were 12,058 men and 3,357 women in our analysis, accounting for 78.2% and 21.8% of the cohort, respectively.

BASELINE CHARACTERISTICS. The baseline characteristics in men and women are shown in Table 1. Women were on average 2 years older than men, had higher SBP, and had a higher heart rate. There was no significant difference in body mass index, but women were more often obese (33.4% women vs. 29.2% men).

PRE-EXISTING COMORBIDITIES. Apart from hypertension (70.6% women vs. 65.5% men) and clinically significant valvular disease (5.3% vs. 4.6%), women were less likely to have a history of major comorbid conditions such as atrial fibrillation (AF) (32.6% vs. 36.4%), previous MI (30.0% vs. 45.4%), and stroke (7.4% vs 8.0%). As well as having a lower prevalence of coronary artery disease (CAD), women had a much lower rate of prior coronary revascularization.

Among non-CV comorbidities, women had a similar prevalence of diabetes (31.0% vs. 31.6%) but a lower prevalence of chronic obstructive pulmonary disease (8.5% vs. 13.1%). Women were also less likely to be current smokers (6.2% vs. 15.8%) and had lower intake of alcohol.

In the EQ-5D-3L state of health score, women were much more likely to report moderate to extreme anxiety or depression (44.0% in women vs. 29.0% in men; $p < 0.0001$) (PARADIGM-HF trial only). This was especially true of women with an ischemic etiology (Online Tables 1 and 2).

HF CHARACTERISTICS AND INVESTIGATIONS AT BASELINE. As shown in Table 2, fewer women had been living with a diagnosis of HF for >5 years (27.5% vs. 31.4%) and had been hospitalized for HF less often than men (58.1% vs. 62.3%). They were also less likely to have an ischemic etiology (50.0% vs. 60.5%).

Women had more symptoms than men, with a higher prevalence of dyspnea on effort (88.7% vs. 84.7%), paroxysmal nocturnal dyspnea (7.1% vs. 4.3%), and more evidence of congestion (peripheral edema, jugular venous congestion, and rales).

Women also had a slightly but significantly higher LVEF (29.6% vs. 28.8%), but median NT-proBNP was not significantly different (women 1,448 pg/ml vs. men 1,406 pg/ml) and B-type natriuretic peptide (PARADIGM-HF trial only) was lower in women than men: 234 (interquartile range: 142 to 430) pg/ml versus 259 (interquartile range: 157 to 478) pg/ml ($p < 0.0001$). Other biomarkers (measured in the PARADIGM-HF trial only) are shown in Online Tables 3 and 4.

Mean eGFR was lower in women and a higher proportion of women had an eGFR <60 ml/min/1.73 m^2. Women were more likely to be in a higher NYHA functional class and had lower (worse) median KCCQ scores. Most of the individual KCCQ domain scores were also lower in women (**Figure 1**, Online Figure 1). The EQ-5D-3L state of health score (PARADIGM-HF trial only) showed large differences between women and men in their mobility, ability to undertake usual activities, and ability to self-care (washing and dressing) (Online Table 1).

TREATMENT AT BASELINE. The rates of use of a diuretic, beta-blocker, and MRA were very similar in women and men (**Table 2**). Women were slightly more likely to receive digitalis (32.4% vs. 30.6%) and ARBs (16.4% vs. 11.9%) compared with men, and less likely to receive an ACE inhibitor (84.7% vs. 88.7%). The difference in rates of use of statins, aspirin, and anticoagulants were larger (47.6% vs. 56.3%, 46.4% vs. 53.0%, and 26.7% vs. 32.4% in women and men, respectively).

Women were less likely to have received a device than men: implantable cardioverter-defibrillator (8.6% vs. 16.6%) and cardiac resynchronization therapy (4.1% vs. 6.9%). Women were also less likely to have received influenza vaccination in the 12 months before enrollment (19.2% vs. 21.6%; $p = 0.024$), to have been enrolled in a disease management program (13.3% vs. 15.8%; $p = 0.008$) or to have been prescribed an exercise regimen (15.0% vs. 18.1%; $p = 0.002$) (PARADIGM-HF trial only) (Online Table 5). Treatment during follow-up is shown in Online Table 6.

OUTCOMES. Women had a significantly lower rate of the primary composite outcome (9.88 vs. 12.52 events per 100-person years), with an adjusted HR of 0.75 (95% confidence interval [CI]: 0.69 to 0.81), as shown in **Table 3 and Figure 2**. Looking at the components of this composite, the rate and risk of first hospitalization for HF was also lower in women (adjusted HR: 0.80; 95% CI: 0.72 to 0.89).

TABLE 2 Continued

	Women (n = 3,357)	Men (n = 12,058)	p Value
Digitalis	1,089 (32.4)	3,692 (30.6)	0.048
Beta-blocker	3,075 (91.6)	11,168 (92.6)	0.049
MRA	1,555 (46.3)	5,718 (47.4)	0.2599
ACE inhibitor	2,842 (84.7)	10,697 (88.7)	<0.0001
ARB	551 (16.4)	1,434 (11.9)	<0.0001
CCB§	330 (9.8)	1,035 (8.6)	0.0245
Statins	1,598 (47.6)	6,787 (56.3)	<0.0001
Aspirin	1,557 (46.4)	6,393 (53.0)	<0.0001
Anticoagulants	897 (26.7)	3,906 (32.4)	<0.0001
In patients with atrial fibrillation on ECG	67.1	71.2	0.029
In patients with atrial fibrillation history	60.6	66.6	<0.001
CHA_2DS_2-VASc score ≥2	67.1	71.5	0.019
Pacemaker	310 (9.2)	1,490 (12.4)	<0.0001
ICD (including CRT-D)	290 (8.6)	2,001 (16.6)	<0.0001
ICD only	196 (5.8)	1,371 (11.4)	<0.0001
CRT-P or CRT-D	137 (4.1)	830 (6.9)	<0.0001

Values are n (%), mean ± SD, median (interquartile range), or %. *13 were missing. †Proportion of total population. ‡Sixty-eight others or other combinations. §Dihydropyridine calcium-channel blocker (CCB).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; JVD = jugular venous distension; KCCQ = Kansas City Cardiomyopathy Questionnaire; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; PND = paroxysmal nocturnal dyspnea; RBBB = right bundle branch block.

The risk of CV death was also lower, as were each of the 2 major modes of CV death (i.e., sudden death and pump failure death). The adjusted HRs for these outcomes (0.65 to 0.70) were lower than for HF hospitalization. Interestingly, the risk of non-CV death was also lower in women and, as a result, so was the risk of all-cause death (adjusted HR for non-CV death: 0.66; 95% CI: 0.52 to 0.83; HR for all-cause death: 0.68; 95% CI: 0.62 to 0.74).

When outcomes were examined according to investigator-reported etiology (nonischemic vs. ischemic), men with both nonischemic and ischemic etiology did worse than women in the corresponding groups did (Online Table 7, Online Figure 2). Among men, those with an ischemic etiology had higher mortality rates than did individuals with a nonischemic etiology. However, among women mortality did not vary by etiology (i.e., the "protection" conferred by a nonischemic background in men [compared with an ischemic substrate] seemed to be absent in women) (Online Figure 2).

Although women were less likely to have a fatal or nonfatal MI than men (1.08 vs. 1.33 events per 100 person-years), the rate of stroke was higher in women (1.54 vs. 1.19 events per 100 person-years).

RECURRENT EVENTS. During a median follow-up of 908 (interquartile range: 1 to 2,285) days, there was a total of 3,006 hospitalizations for any cause in women and 13,641 hospitalizations for any cause in men (**Table 4**). Of these, 750 (25.1%) were due to HF in women and 3,569 (26.2%) were due to HF in men. Among women, 4.3% had >1 hospitalization for HF and the same was true for 6.4% of men (Online Table 8).

The adjusted IRR for recurrent HF hospitalization for women compared with men was 0.69 (95% CI: 0.61 to 0.79). The IRRs for CV hospitalization (0.73; 95% CI: 0.67 to 0.79), all-cause hospitalization (0.75; 95% CI: 0.71 to 0.81), and non-CV hospitalization (0.82; 95% CI: 0.75 to 0.89) were higher than for HF hospitalization.

DISCUSSION

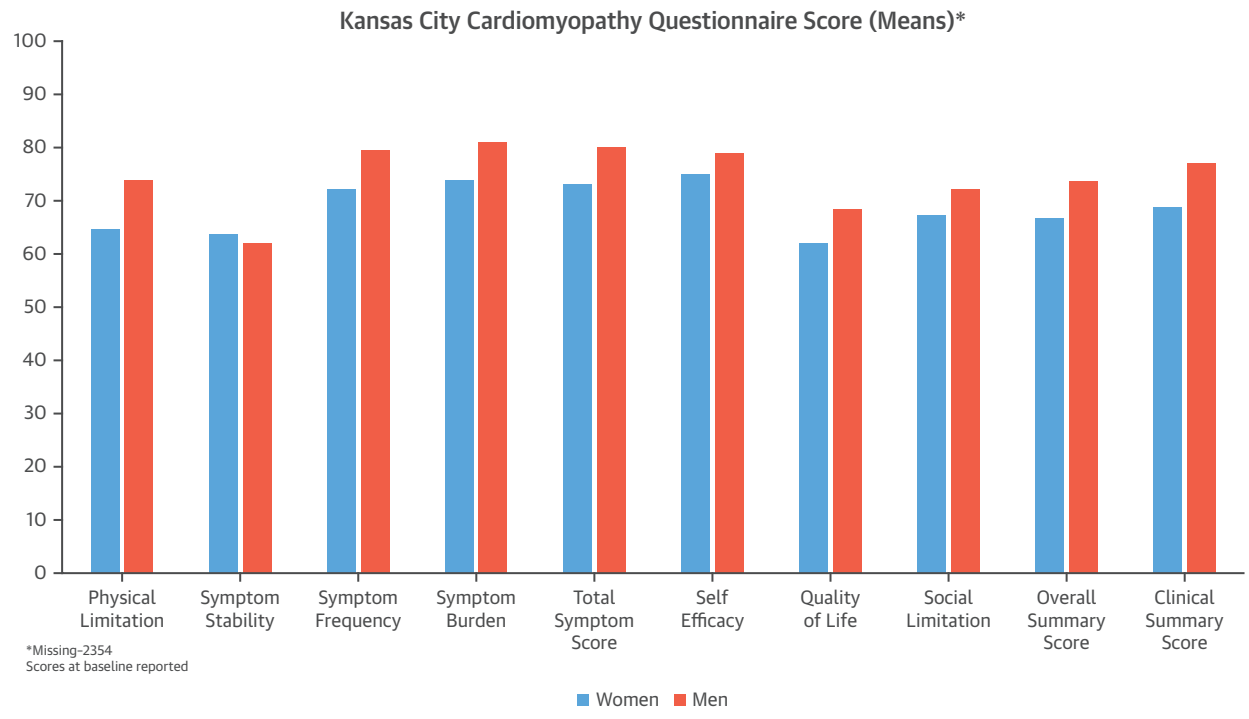
In an analysis of 15,415 patients, including 3,357 women from 55 countries, we confirmed many known differences between men and women (**Central Illustration**) (2-4,7). In addition, we identified some new differences and, importantly, showed a narrowing of previously highlighted gaps, especially in pharmacological treatment (although anticoagulants were still underutilized in women). However, problems persist—women were undertreated with devices and less likely to receive influenza vaccination, be enrolled in a disease-management program, or be prescribed an exercise regimen.

BASELINE CHARACTERISTICS. Women remain the minority of patients with HFrEF enrolled in trials because HFrEF is more common in men. Women are older than men and less likely to have an ischemic etiology. Both physician-assessed (NYHA functional class) and patient-reported (KCCQ) severity of HF was greater in women than men. Women had more symptoms and signs of HF (and congestion), despite having more recently diagnosed HF, higher mean LVEF, and similar NT-proBNP (and even lower B-type natriuretic peptide). Prior HF hospitalization was less common in women than men. Looking at other markers of severity, more women had an eGFR <60 ml/min/1.73 m^2 and their SBP was slightly higher than in men. The most striking difference was the large (10-point) difference in the median KCCQ score. This is notable given that older patients, generally report better HRQL, compared with younger patients, and women were older than men (19). To explore what lay behind this difference we examined different KCCQ domains. The largest difference was in "physical limitations." This was supported by the state of health score (from the EQ-5D-3L), which showed striking differences between women and men in mobility, ability to undertake usual activities, and ability to self-care. The reasons for these differences in symptoms and HRQL between men and women are not clear, as they do not seem to be explained by major differences in physiological markers of HF severity (see the previous text) or by comorbidities (see the following text). Clearly, however, HF appears to have a greater impact on the lives of women, compared with men, and women live with more symptoms and worse disease-specific and general quality of life than men do.

The pattern of comorbidity differed strikingly between men and women. Given their less frequent ischemic etiology, women had fewer manifestations of CAD and atherothrombotic disease more generally. Conversely, a history of hypertension was more common in women. Obesity was also more common although diabetes was not. AF was less common in women and chronic obstructive pulmonary disease much less common, in keeping with the lower rate of previous or current smoking in women (although this again highlights the greater dyspnea experienced by women). Although the prevalence of anemia was similar between men and women, mean hemoglobin in women was 12 g/l, lower than in men. A remarkable proportion of women (45%) self-reported moderate-to-extreme anxiety or depression using the EQ-5D-3L score (especially if their etiology was ischemic). This may suggest HF has a greater psychological impact on women than on men. These findings of worse symptoms and more physical and psychological disability related highlight the underutilization of disease-management programs and exercise regimens in women, the interventions likely to be particularly helpful for these problems.

TREATMENT AT BASELINE. Prior treatment with a renin-angiotensin system blocker was required in the PARADIGM-HF and ATMOSPHERE trials, and women were more often treated with an ARB (as opposed to an ACE inhibitor) compared with men, probably reflecting higher likelihood of cough with ACE inhibitor in women (20,21). Beta-blocker use was also required, unless not tolerated or contraindicated, and was similar between sexes. MRA use was at the investigators' discretion and was similar between sexes. Although women had more congestion than men did, use of diuretic was similar between the sexes, as was use of digoxin, even though women had less AF, and despite digoxin use being associated with greater mortality in women (22). Overall therefore, and contrary to previous reports, we did not find evidence of significant undertreatment of women with most HF medications, except, perhaps diuretics

FIGURE 1 **Scores for Each Individual Domain of the Kansas City Cardiomyopathy Questionnaire in Men and Women With Heart Failure With Reduced Ejection Fraction at Baseline**



Bars show mean score for each domain or summary score. The y-axis represents score of a possible 100 (with a lower score representing worse quality of life). Women reported lower (worse) scores in all domains except symptom stability, when compared with men.

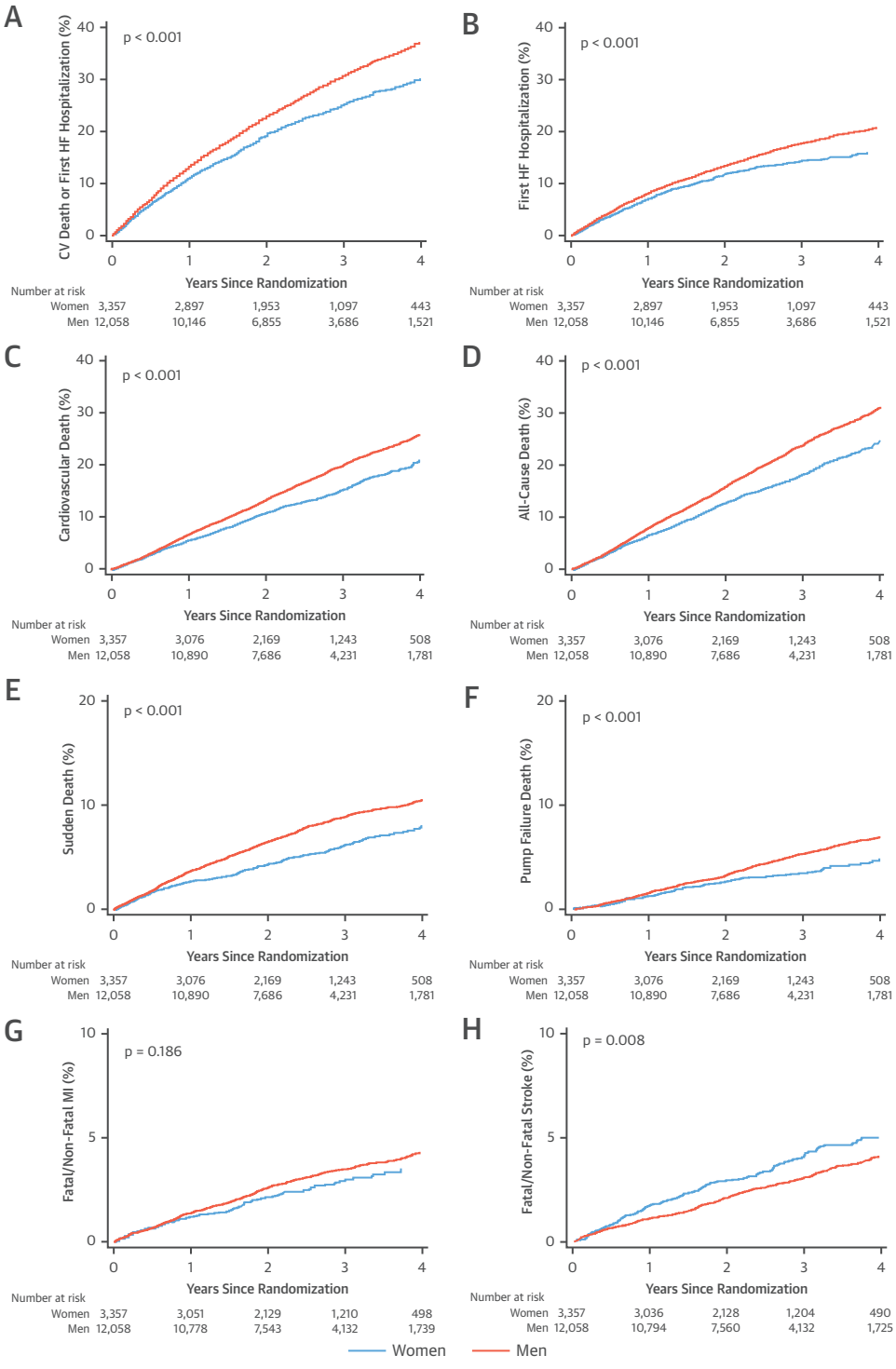
TABLE 3 **Clinical Outcomes in Men and Women With HFrEF**

	Total Events		Events per 100 Person-Years (95% CI)		Women vs. Men	
	Women (n = 3,357)	Men (n = 12,058)	Women (n = 3,357)	Men (n = 12,058)	Unadjusted HR (95% CI) p Value	Adjusted HR (95% CI) p Value
Primary composite outcome	808 (24.1)	3,592 (29.8)	9.88 (9.22–10.59)	12.52 (12.12–12.94)	0.79 (0.73–0.85) <0.001	0.75 (0.69–0.81) <0.001
First hospitalization for HF*	460 (13.7)	2,059 (17.1)	5.63 (5.13–6.16)	7.18 (6.87–7.50)	0.81 (0.74–0.90) <0.001	0.80 (0.72–0.89) <0.001
CV death	508 (15.1)	2,364 (19.6)	5.74 (5.27–6.27)	7.56 (7.26–7.87)	0.74 (0.67–0.81) <0.001	0.70 (0.63–0.77) <0.001
Sudden death	196 (5.8)	1,022 (8.5)	2.22 (1.93–2.55)	3.27 (3.07–3.47)	0.67 (0.57–0.78) <0.001	0.65 (0.56–0.76) <0.001
Pump failure death	119 (3.5)	616 (5.1)	1.35 (1.12–1.61)	1.97 (1.82–2.13)	0.70 (0.57–0.85) <0.001	0.67 (0.55–0.82) <0.001
Non-CV death	93 (2.8)	476 (3.9)	1.05 (0.86–1.29)	1.52 (1.39–1.66)	0.71 (0.57–0.89) 0.003	0.66 (0.52–0.83) <0.001
All-cause death	601 (17.9)	2,840 (23.6)	6.80 (6.27–7.36)	9.08 (8.75–9.42)	0.73 (0.67–0.80) <0.001	0.68 (0.62–0.74) <0.001
Fatal/nonfatal MI	94 (2.8)	412 (3.4)	1.08 (0.88–1.32)	1.33 (1.21–1.47)	0.86 (0.69–1.08) 0.186	0.79 (0.63–1.00) 0.048
Fatal/nonfatal stroke	134 (4.0)	368 (3.1)	1.54 (1.30–1.82)	1.19 (1.08–1.32)	1.31 (1.07–1.59) 0.008	1.22 (0.99–1.50) 0.062

Values are n (%), unless otherwise indicated. All outcomes have been adjusted for randomized treatment and region at baseline. Adjusted model has been adjusted for age, heart rate, systolic blood pressure, NT-proBNP, BMI, NYHA functional class, LVEF, and eGFR. All outcomes were tested for competing risks of all-cause and noncardiovascular (non-CV) death. Sudden death was tested for competing risk of all nonsudden deaths and pump failure death for all non–pump failure deaths. Non-CV death was tested for competing risk of CV death. *Additional adjusted for previous heart failure hospitalization.

Abbreviations as in Table 2.

FIGURE 2 Clinical Outcomes in Men and Women With Heart Failure With Reduced Ejection Fraction



Cumulative event curves for **(A)** primary composite outcome, **(B)** hospitalization for heart failure (HF), **(C)** cardiovascular (CV) death, **(D)** all-cause death (Kaplan-Meier), **(E)** sudden death, **(F)** pump failure death, **(G)** fatal or nonfatal myocardial infarction (MI), and **(H)** fatal or nonfatal stroke. The risk table below the graphs shows the numbers at risk of the event of interest. Women were at reduced risk for all outcomes except stroke when compared with men. All p values were unadjusted (Fine and Gray).

TABLE 4 Analysis of Repeat Hospitalizations in Men and Women With HFrEF (Negative Binomial Model)

	Total Events		Events per 100 Person-Years (95% CI)		Women vs. Men	
	Women (n = 3,357)	Men (n = 12,058)	Women (n = 3,357)	Men (n = 12,058)	Unadjusted IRR (95% CI) p Value	Adjusted IRR (95% CI) p Value
HF hospitalization	750	3,569	8.48 (7.89–9.11)	11.40 (11.04–11.79)	0.70 (0.62–0.80) <0.001	0.69 (0.61–0.79) <0.001
CV hospitalization	1,719	8,017	19.44 (18.54–20.38)	25.62 (25.07–26.19)	0.74 (0.68–0.81) <0.001	0.73 (0.67–0.79) <0.001
Non-CV hospitalization	1,287	5,624	14.55 (13.78–15.37)	17.98 (17.51–18.45)	0.87 (0.80–0.95) 0.001	0.82 (0.75–0.89) <0.001
All-cause hospitalization	3,006	13,641	33.99 (32.79–35.22)	43.60 (42.87–44.34)	0.79 (0.74–0.84) <0.001	0.75 (0.70–0.81) <0.001

Values are n, unless otherwise indicated. Incident rate ratios (IRRs) adjusted for age, previous HF hospitalization, heart rate, systolic blood pressure, NT-proBNP, BMI, NYHA functional class, LVEF, and eGFR.

Abbreviations as in Table 2 and 3.

which appeared relatively underused given the finding of more congestion in women (7). This underuse of diuretics, overuse of digoxin, and underutilization of disease-management programs and exercise prescription in women brings to focus potentially important questions about the role of patient sex in doctor-patient communication, prescribing and medical practice more generally (22-26). Do doctors fail to appreciate the impact of HF in women compared with men or are women less able to communicate the severity of the impact of their illness? We are not aware of prior report of lower enrollment of women in disease management and exercise programs but similar underutilization of cardiac rehabilitation has been reported and the explanation is likely multifactorial, and includes the older age of women, comorbidity, and socioeconomic factors (27). Women may also be more likely to withdraw from such programs even though trials such as the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial have shown potentially greater benefit from rehabilitation and exercise in women compared with men (28,29).

In contrast to drugs for HF, device use, especially implantable cardioverter-defibrillator use, was much less in women than in men. Further analysis according to etiology, NYHA functional class, LVEF, rhythm, and QRS duration or morphology did not account for disparity in device use (data not shown). The lower use of cardiac resynchronization therapy in women is especially notable, as that this intervention may be even more effective in women than men and given that left bundle branch block is more common in women (as confirmed in the present study), often with a narrower QRS duration than in men (30).

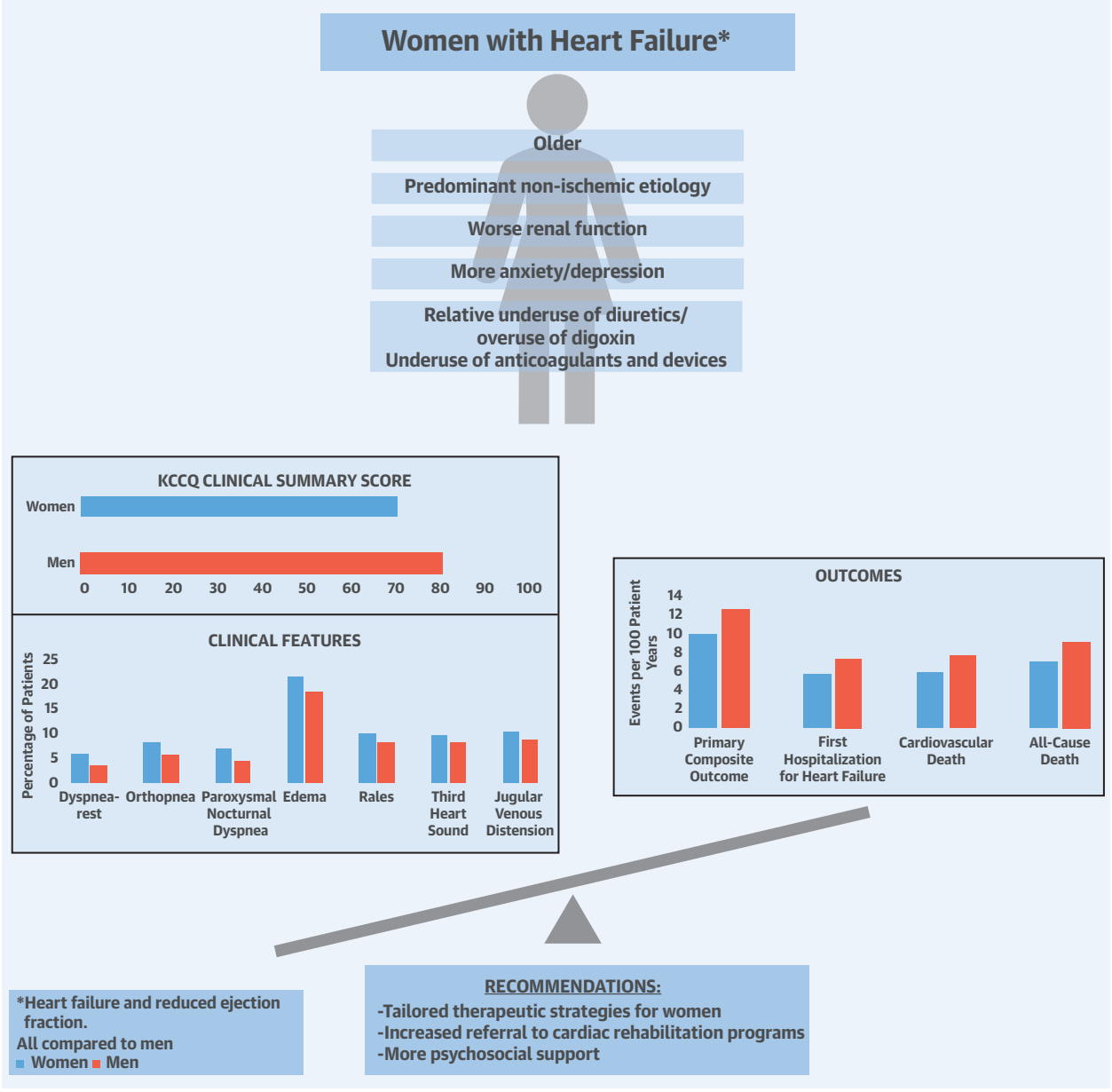
Anticoagulant use was significantly less common in women with a history of AF (and in those with AF on their baseline electrocardiogram), reflecting registry and "real-world" data showing underuse of these drugs in women (31). Differences in other pharmacological therapies appeared to reflect differences in comorbidities (e.g., the greater use of statins and aspirin in men likely reflected the higher prevalence of CAD in men).

OUTCOMES. As has been shown previously, women had better outcomes than men (2,3,7). However, we did analyses additional to those carried out in previous clinical trial datasets. Because the ATMOSPHERE and PARADIGM-HF trials were more contemporary than prior studies, we had a measurement of NT-proBNP and were able to adjust for this most powerful of all prognostic variables in HF. Given the lower mortality rate in women than men, we also analyzed hospitalization for HF, taking account of the competing risk of death (and examined the total burden of HF hospitalizations by examining repeat events).

Even after adjusting for NT-proBNP, and other prognostic variables, women remained less likely to die than men. Indeed, the differential increased somewhat so that the adjusted risk of death from any cause was 32% lower in women, greater than that identified in the largest prior sex-based analysis in HF from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) trial (7). We also looked at the 2 major modes of CV death in HFrEF (i.e., sudden death and death from pump failure or progressive HF). Both were less common in women (and the lower risk was proportionally similar for each, in women compared with men). The explanation for this is unknown, although 1 possibility is the difference that has been described in cardiac remodeling between men and women, possibly aggravated by more unfavorable remodeling in response to ischemic injury in men (with a higher prevalence of CAD in men) (32,33).

In contrast to death, the lower risk of a first HF hospitalization was less marked: women were 20%

CENTRAL ILLUSTRATION **Women With Heart Failure With Reduced Ejection Fraction**



Dewan, P. et al. J Am Coll Cardiol. 2019;73(1):29–40.

This schematic shows that women with heart failure with reduced ejection fraction (in comparison with men) are older, are more likely to have a nonischemic etiology, have worse renal function, have more congestion, and have more psychological morbidity. Even though they have better survival and have fewer hospitalizations for heart failure, they have a greater symptom burden and a lower quality of life. Tailored therapeutic approaches in women with sex-sensitive person-centered care, more frequent referral to cardiac rehabilitation programs, and more psychological support may be required to rectify these problems. KCCQ = Kansas City Cardiomyopathy Questionnaire.

less likely to be hospitalized for HF than men were. This more modest relative risk may be because we accounted for the substantial competing risk of death. Interestingly, the lower risk of HF hospitalization in women was apparent for second and subsequent (and not just first) admissions, and the sex difference was larger when repeat admissions were examined. Moreover, the risk of hospitalization for any CV

reason and for any reason at all was lower in women (although the largest sex-difference was seen for HF and the smallest for all-cause hospitalization). The absolute differences were substantial when repeat events were considered: 3, 6, and 10 fewer admissions per 100 person-years of follow-up in women, compared with men, for HF, any CV reason, and all causes, respectively.

Collectively, these differences in symptoms, HRQL, mortality, and hospitalization highlight some interesting sex-related paradoxes. Intuitively, worse symptoms or HRQL might have been expected to be associated with higher (rather than lower) rates of hospitalization. Similarly, better survival might have led to a higher lifetime burden of hospital admissions (especially if longevity was associated with greater symptoms and worse HRQL). In both cases the converse was observed, with women living longer than men but experiencing poorer HRQL during their additional years of life. The explanation for the disconnect between symptoms or HRQL and hospital admission rates is uncertain. Is it just about women's perception of the impact of their disease or are there sex-related confounders not measured in this study (e.g., differences in access to health care, less caregiver support or living alone, socioeconomic and educational factors, and less proactive seeking of help)?

More expected from the difference in background CAD, the risk of MI was lower in women than in men. Conversely, the risk of stroke was greater and may, in part, be explained by the lower rate of anticoagulation in women, as mentioned previously, as well as the higher prevalence of hypertension in women.

There are 2 other recent reports about sex-related differences in HF trials. The STICH (Surgical Treatment for Ischemic Heart Failure) trial enrolled 148 women between 2004 and 2007 and the EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy) trial enrolled 224 women between 2008 and 2013 (34,35). Apart from the small number of women in both these trials, it is difficult to draw any general conclusions because patients were also highly selected for specific interventions and the EchoCRT trial was stopped early for harm, with only 64 primary events among women.

STUDY STRENGTHS AND LIMITATIONS. The patients enrolled were selected and are potentially better treated than are those in the "real world." We focused on HFrEF, whereas many women with HF have preserved LVEF. We did not have serial assessments of left ventricular structure and function. Our study has strengths as well. It is the only large, contemporary, clinical trial dataset with many women. In trials, patients are well characterized, and outcomes are carefully collected and adjudicated. Because of the increasing globalization of trials, we were able to report the most geographically representative analysis of women with HFrEF to date.

CONCLUSIONS

While women with HFrEF have fewer comorbidities, better survival, and lower rates of hospitalization, they have more symptoms and worse HRQL than men do. They also report much more anxiety or depression. Women appeared relatively undertreated with diuretics given their greater evidence of congestion, and devices were underutilized more in women than in men. Women were less often referred to a disease management program or prescribed an exercise regimen. Although women with HFrEF live longer than men do, their additional years of life are of poorer quality, with greater self-reported psychological and physical disability. This different sex-related experience of HFrEF is unexplained and it is uncertain whether physicians recognize it. Women continue to receive suboptimal treatment, compared with men.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Women with HFrEF are generally older and have a greater symptom burden and more impaired quality of life, but less frequent hospitalization and longer survival than men with this condition.

TRANSLATIONAL OUTLOOK: Future studies should address these differences in evaluating therapeutic strategies for women with HFrEF. The lower prevalence of HFrEF in women is 1 factor limiting representation of women in clinical trials, while lower event rates in women than men compounds the challenge of assessing the relative risks and benefits of these interventions.

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KEY WORDS heart failure, sex, women

APPENDIX For supplemental tables and figures, please see the online version of this paper.